



General

Guideline Title

Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation.

Bibliographic Source(s)

Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, Hakim H, Santolaya M, Castagnola E, Davis BL, Dupuis LL, Gibson F, Groll AH, Gaur A, Gupta A, Kebudi R, Petrilli S, Steinbach WJ, Villarroel M, Zaoutis T, Sung L. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation. Toronto (Ontario): The Hospital for Sick Children; 2012 Sep. 52 p. [199 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The strength of recommendation (1-2) and quality of evidence (A-C) are defined at the end of the "Major Recommendations" field.

Section 1: Initial Presentation of Fever and Neutropenia (FN)

Question: *What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?*

Recommendation: Adopt a validated risk stratification strategy (see Table 2 in the original guideline document) and incorporate it into routine clinical management (1C, strong recommendation, low-quality evidence).

Question: *What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?*

Recommendations: Obtain blood cultures at the onset of FN from all lumens of central venous catheters (CVCs) (1C, strong recommendation, low-quality evidence).

Consider peripheral blood culture concurrent with obtaining CVC cultures (2C, weak recommendation, low-quality evidence).

Consider urinalysis and urine culture in patients for whom a clean-catch, midstream specimen is readily available (2C, weak recommendation, low-quality evidence).

Obtain chest radiography only in symptomatic patients (1B, strong recommendation, moderate-quality evidence).

Question: *What empiric antibiotics are appropriate for children with high-risk FN?*

Recommendations: Use monotherapy with an anti-pseudomonal β -lactam or a carbapenem as empiric therapy in pediatric high-risk FN (1A, strong recommendation, high-quality evidence).

Reserve addition of a second Gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (1B, strong recommendation, moderate-quality evidence).

Question: *In children with low-risk FN, is initial or step-down outpatient management as effective and safe as inpatient management?*

Recommendation: In children with low-risk FN, consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (2B, weak recommendation, moderate-quality evidence).

Question: *In children with low-risk FN, is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?*

Recommendation: In children with low-risk FN, consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (2B, weak recommendation, moderate-quality evidence).

Section 2: Ongoing Management of FN Excluding Empiric Antifungal Therapy

The following section applies to children with FN who have already been started on empiric antibiotic therapy and observed for some period of time by either healthcare providers, parents, or both.

Question: *When and how should the initial empiric antibiotic therapy be modified during the pediatric FN episode?*

Recommendations: In patients who are responding to initial empiric antibiotic therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (1B, strong recommendation, moderate-quality evidence).

Do not modify the initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable (1C, strong recommendation, low-quality evidence).

In children with persistent fever who become clinically unstable, escalate the initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria (1C, strong recommendation, very low-quality evidence).

Question: *When can empiric antibiotics be discontinued in patients with low- and high-risk FN?*

Recommendations: Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours and who have evidence of marrow recovery (1C, strong recommendation, low-quality evidence).

Consider discontinuation of empiric antibiotics at 72 hours in low-risk patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured (2B, weak recommendation, moderate-quality evidence).

Section 3: Empiric Antifungal Treatment

Question: *What clinical parameters can classify pediatric patients with persistent FN as high risk or low risk for invasive fungal disease (IFD)?*

Recommendation: Patients at IFD high-risk are those with acute myeloid leukemia, relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and allogeneic hematopoietic stem cell transplantation recipients with persistent fever despite prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (>10 days). All others should be categorized as IFD low-risk (1B, strong recommendation, moderate-quality evidence).

Question: *What clinical features, laboratory tests, imaging studies, and procedures (such as bronchoalveolar lavage [BAL] and biopsy) are useful to identify a fungal etiology for persistent/recurrent FN despite broad-spectrum antibiotics?*

Recommendations: Consider prospective monitoring of serum galactomannan (GM) twice weekly in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis (2B, weak recommendation, moderate-quality evidence).

In IFD low-risk patients, do not implement routine GM screening (1C, strong recommendation, low-quality evidence).

Consider GM in BAL and cerebrospinal fluid to support the diagnosis of pulmonary or central nervous system aspergillosis (2C, weak recommendation, low-quality evidence).

In children, do not use β -D-glucan (BG) testing for clinical decisions until further pediatric evidence has accumulated (1C, strong recommendation, low-quality evidence).

In IFD high-risk children with persistent FN beyond 96 hours, perform evaluation for IFD. Evaluation should include computerized tomography (CT) of the lungs and targeted imaging of other clinically suspected areas of infection (1B, strong recommendation, moderate-quality evidence). Consider CT of the sinuses in children 2 years of age or older (2C, weak recommendation, low-quality evidence).

Questions: *When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?*

Recommendations: In neutropenic IFD high-risk children, initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (≥ 96 hours) broad-spectrum antibacterial agents (1C, strong recommendation, low-quality evidence).

In neutropenic IFD low-risk children, consider empiric antifungal therapy in the setting of persistent FN (2C, weak recommendation, very low-quality evidence).

Use either caspofungin or liposomal amphotericin B (L-AmB) for empiric antifungal therapy (1A, strong recommendation, high-quality evidence).

Definitions:

Strength of Recommendation

1 = Strong

2 = Weak

Quality of the Evidence

A = High

B = Moderate

C = Low or very low

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Fever and neutropenia

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Oncology

Pediatrics

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To develop an evidence-based guideline for the empiric management of pediatric fever and neutropenia

Target Population

Children with cancer and/or undergoing hematopoietic stem cell transplantation who have fever and neutropenia

Interventions and Practices Considered

Diagnosis/Evaluation

1. Risk stratification strategy
2. Clinical, laboratory, and imaging studies
 - Blood culture
 - Urinalysis and urine culture
 - Chest radiography (CXR)
3. Evaluation for invasive fungal disease (IFD)
 - Monitoring serum galactomannan (GM) in bronchoalveolar lavage (BAL) and cerebrospinal fluid, if indicated
 - Computed tomography (CT) of the lungs or other suspected area of infection, including sinuses (if age 2 or older)

Treatment/Management

1. Monotherapy of empiric antibiotics
 - Antipseudomonal β -lactam
 - Carbapenem
2. Reservation of addition of a second Gram-negative agent or glycopeptide for unstable patient, resistant infection, or centers with a high rate of resistant pathogens
3. For low-risk fever and neutropenia (FN)
 - Initial or step-down outpatient management
 - Oral antibiotics
4. Ongoing management of FN excluding antifungal therapy

- Modification of antibiotic therapy
 - Discontinuation of empiric antibiotics if negative blood culture(s), afebrile for 24 hours, and evidence of marrow recovery
5. Empiric antifungal therapy: caspofungin or liposomal amphotericin B

Major Outcomes Considered

- Death
- Persistent fever/time to resolution of fever
- Sepsis syndrome
- Clinical deterioration/intensive care unit admission
- Serious medical complication
- Microbiologically or clinically documented infection
- Secondary infection including breakthrough bacteremia
- Re-admission
- Recurrence of infection/fever
- Modification of initial empiric antibiotics
- Quality of life
- Toxicity
- Resolution of fever and neutropenia with or without modification of therapy
- Breakthrough fungal infection (proven or probable yeast or mold infection)
- Development of pulmonary infiltrates
- Fever unresponsive to antibiotic treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

For each question, systematic reviews of the published literature were conducted until March 2011 (available from [The Hospital for Sick Children Web site](#)). Empiric treatments focused on pharmacological interventions and did not include therapies such as growth factors. A pragmatic, hierarchical approach was undertaken in the search. For all questions, systematic reviews of primary studies were sought and results in children were identified. In the event that there were little or no pediatric data to inform recommendations on a specific health question, evidence from adult studies and combined adult and pediatric studies was considered. Where there were no studies of the highest quality or where they were few in number, for example, few randomized controlled trials, designs with a greater risk of bias such as observational studies were subsequently searched for and reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of the Evidence

A = High

B = Moderate

C = Low or very low

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

For each question, the working group compiled evidence summaries. Lack of pediatric data was accounted for in the quality description of evidence (i.e., indirect evidence). Sample sizes were limited for some synthesized outcomes and thus, 95% confidence intervals (CIs) were provided to facilitate interpretation.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to generate summaries and evidence was classified as high, moderate, low, or very low based upon methodologic considerations. The key methodological elements are in study design, consistency of the body of evidence, directness of the studies to the question under consideration, and limitations in the conduct of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Previously validated procedures for creating evidence-based guidelines were followed and the Appraisal of Guidelines Research & Evaluation II instrument was used as a framework. The International Pediatric Fever and Neutropenia Guideline Panel was first formed in October 2010. The group included representation from oncology, infectious disease, nursing, pharmacy, and a patient advocate from 10 different countries (see Appendix 1 in the original guideline document). Members were divided into working groups that addressed each of the three major sections (initial presentation, ongoing management, and empiric antifungal therapy).

Formulating Questions, Rating Importance of Outcomes, and Development of Evidence Profiles

Each working group developed the key clinical questions to be addressed by the guideline and identified and rated the importance of outcomes relevant to the questions on a 9 point scale (see Appendix 2 of the original guideline document). Ratings of 7–9 indicated that the outcome was critical for a decision or recommendation; 4–6 indicated that it was important, and 1–3 indicated that it was not important. The median ratings from working group members established the importance of the outcomes (see Appendix 2 of the original guideline document) and guided recommendations.

Based upon the evidence summaries, each working group developed recommendations which considered health benefits, side effects, risks, and costs.

Panel Meeting and Development of Recommendations

The first meeting of the Panel was held on October 21st, 2010 (Boston, MA) to plan guideline development. A second meeting was held on September 18th, 2011 (Chicago, IL) to discuss the results of the evidence summaries and each working group's preliminary recommendations. Following several conference calls, revised documents were then circulated.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 = Strong

2 = Weak

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Once the Panel had approved the final version, review by seven external expert reviewers was undertaken. A final revised version was created on February 17, 2012.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation

Potential Harms

- Adverse effects associated with treatment, including nephrotoxicity
- A single center retrospective study of computed tomography (CT) scans in pediatric patients with prolonged fever and neutropenia (≥ 96 hours) demonstrated the potential usefulness of repeated imaging studies. However, the potential benefits of repeated CT scans should be balanced against the cumulative radiation exposure from this approach.
- It is important to note that some specific antibacterial agents (such as piperacillin-tazobactam) may cause false-positive serum galactomannan (GM) results in pediatric and adult patients.

Qualifying Statements

Qualifying Statements

The guideline panel has created an evidence-based guideline for the management of pediatric fever and neutropenia (FN). Some recommendations are similar to those of adult guidelines, such as choice of empiric antibacterials and criteria for their modification. Some similar recommendations

have benefitted from a pediatric-specific focus, such as consideration of outpatient management and oral antibacterial therapy. However, there are key distinctions. For example, the proposed risk stratification schemas are pediatric specific, and a number of diagnostic tools such as β -D-glucan (BG) testing have pediatric-specific limitations. These factors have an important impact on the care of pediatric patients. Future iterations of this guideline will need to incorporate evolving and emerging evidence as research is conducted in pediatric FN.

Implementation of the Guideline

Description of Implementation Strategy

Considerations for implementation are presented where relevant in the explanations for each recommendation in the original guideline document.

Implementation will require adaptation to the local context and should consider organizational barriers such as available local infrastructure to support different models of care.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Sep

Guideline Developer(s)

The Hospital for Sick Children - Hospital/Medical Center

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Guideline Committee

International Pediatric Fever and Neutropenia Guideline Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this guideline. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Expert Testimony: None Other Remuneration: None

Guideline Endorser(s)

American Society of Clinical Oncology - Medical Specialty Society

American Society of Pediatric Hematology/Oncology - Professional Association

C17 Council - Professional Association

Pediatric Oncology Group of Ontario - Professional Association

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from [The Hospital for Sick Children Web site](#) .

Availability of Companion Documents

The following is available:

- Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, Hakim H, Santolaya M, Castagnola E, Davis BL, Dupuis LL, Gibson F, Groll AH, Gaur A, Gupta A, Kebudi R, Petrilli S, Steinbach WJ, Villarroel M, Zaoutis T, Sung L. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. Short version. J Clin Oncol. 2012 Dec 10;30(35):4427-38. Electronic copies: Available in Portable Document Format (PDF) from [The Hospital for Sick Children Web site](#) .

In addition, appendices (including methodology, evidence profiles, and research gaps) and the search strategies are available from [The Hospital for Sick Children Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 8, 2013. The information was verified by the guideline developer on January 28, 2013.

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